

Rationale for Dantrolene vs. Procainamide for Treatment of Malignant Hyperthermia

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The use of procainamide or procaine for treatment of malignant hyperthermia is commonly recommended. The skeletal muscle relaxant dantrolene has also been indicated for treatment of this complication during anesthesia. In the present study, effects of procainamide and dantrolene were compared in malignant hyperthermia-susceptible (MHS) pigs *in vivo* and on MHS muscle from human patients *in vitro*. The ED₅₀ for dantrolene block of indirectly evoked twitch tension was 0.85 mg/kg in MHS pigs. A final cumulative dose of 2 mg/kg resulted in 68 per cent block of the twitch response. In contrast, procainamide at a final cumulative dose of 14 mg/kg had no effect on twitch response of the MHS pigs. Dantrolene, 3 μ M, *in vitro* (approximately 0.8 mg/kg *in vivo*) was effective in preventing or reversing the abnormal halothane-induced contracture response of human MHS muscle strips. Procainamide, 0.11 mM, a dose approximating clinical levels (about 22 mg/kg), had no effect on basal twitch response or on the abnormal halothane-induced contracture of MHS human muscle. These results confirm the effectiveness of dantrolene and the lack of effectiveness of procainamide in the treatment of malignant hyperthermia. (Key words: Hyperthermia, malignant pyrexia; procainamide; dantrolene. Neuromuscular relaxants: dantrolene.)

THE USE OF PROCAINAMIDE or procaine for the treatment of malignant hyperthermia is commonly recommended.¹⁻⁴ The rationale for treatment of malignant hyperthermia with these agents was derived from studies of isolated muscle *in vitro*⁵⁻⁷ and from their effects on fragmented sarcoplasmic reticulum.⁸ Procainamide was shown to block caffeine-induced contracture of normal skeletal muscle at concentrations of 3-5 mM.^{6,7} Likewise, procainamide (or procaine) has the property of inhibiting caffeine-induced calcium release from fragmented sarcoplasmic reticulum.⁸ The reports of successful treatment of malignant hyperthermia with procainamide in human patients,^{1,3} coupled with the *in vitro* findings cited above, have supported the recommendations for procainamide therapy in malignant hyperthermia. Data suggesting a greater chance of survival from malignant hyperthermia when either procaine or procainamide was associated with treatment of human cases have been reported.⁹ Whether this apparent increase in survival with use of procaine or procainamide relates to treatment of primary or secondary effects remains subjective.

In spite of the apparently logical extrapolation from

in-vitro studies to clinical applications, serious questions have been raised regarding the efficacy of procainamide in treatment of malignant hyperthermia. Procainamide doses of 2 to 5 mM that effectively block caffeine effects *in vitro* would be toxic if applied clinically (approaching 60 g in a 70-kg patient). The failure of procainamide or procaine to prevent or treat porcine malignant hyperthermia has added doubt to the usefulness of these agents for malignant hyperthermia.^{10,11}

A similar mode of experimentation has led to the deduction that the skeletal muscle relaxant, dantrolene, has prophylactic and therapeutic promise for malignant hyperthermia. Dantrolene blocks the abnormal contracture response of malignant hyperthermia-susceptible (MHS) muscle from pig¹² and man,¹³ and has been prophylactically and therapeutically successful in the MHS pig model.^{14,15}

The recent development of an *in-vivo* muscle-twitch preparation in the pig has provided the opportunity to compare the effects of procainamide and dantrolene on indirect toe twitch of MHS pigs. During diagnostic procedures for MHS in human patients, we also had the opportunity to compare the effects of dantrolene and procainamide on human MHS muscle *in vitro*.

Methods

Six female MHS pigs averaging 57 ± 1.3 kg in weight were anesthetized with thiopental, 30 mg/kg, the tracheas were intubated and the animals were ventilated with 100 per cent oxygen. Anesthesia was maintained with thiopental. Rectal temperature, end-tidal carbon dioxide tension, heart rate, EKG, and arterial pressure were continuously monitored. Indirect stimulation of forelimb toe twitch was induced and quantitated as follows.

The most important aspect of the *in-vivo* design was to fix a limb such that movements due to respiration, succinylcholine-induced fasciculations, etc., had no effect on the elicited twitch response. The twitch response could be affected either by movement of the limb in relation to a fixed position of the force transducer, or movement that caused displacement of the stimulating electrodes. These problems were circumvented by the forelimb twitch board (fig. 1). A flat plastic base 45 \times 61 cm and 1 cm thick served as a

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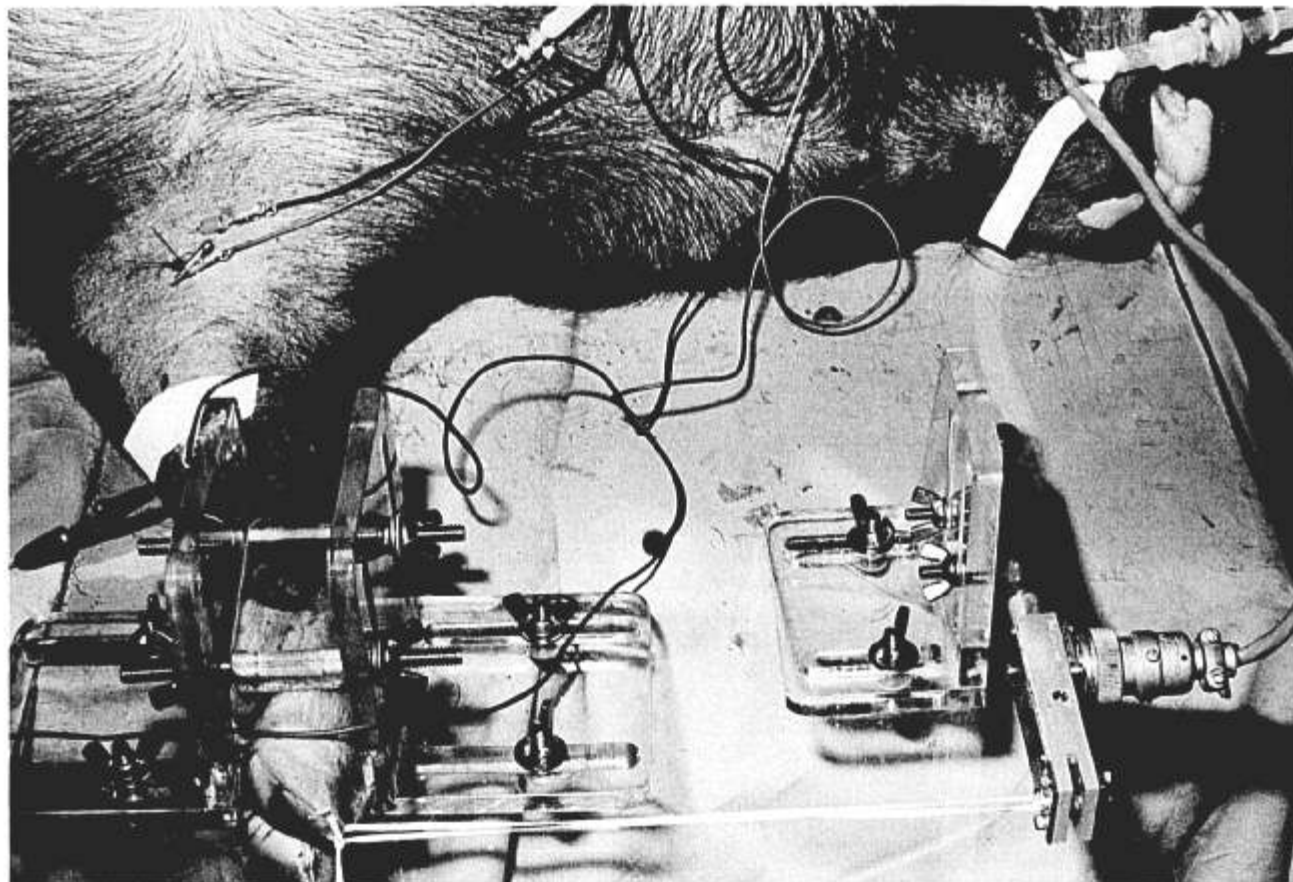


FIG. 1. The apparatus designed to measure toe twitch in the anesthetized pig. The force transducer (lower right) is vertically and horizontally adjustable. The left forelimb is stabilized by two horizontally and vertically adjustable clamps. Two wires positioned high in the axilla of the left forelimb provide median-nerve stimulations. The toe is attached to the force transducer by umbilical tape. A flat, clear plastic baseboard supporting the clamps runs from the bottom of the photograph to lie under the pig's shoulder and head. (Other details under Methods.)

baseboard, which was placed under the shoulder when the pig was in a lateral recumbent position. The baseboard extended out from the pig's body and supported the lower forelimb, while the upper forelimb was supported away from this field. Two adjustable clamps, 10 cm high, were attached near the end of the baseboard away from the animal's body. One clamp supported the force transducer, which could be positioned in three planes, vertically, horizontally and laterally. These adjustments provided the ability to vary tension and to position the transducer for linear twitch response (*i.e.*, parallel and in plane with the adducted toe). The second clamp was used to hold the pig's toe in a fixed plane. The lower front limb was placed in the limb clamp so as to include the metacarpus and carpus and to permit the toes to extend outside the clamp. The limb clamp had three movable supports. The forelimb was placed between two flat clamps that could be adjusted laterally and toward each other in order to fix the limb in optimal

position. A third, vertically adjustable support was fixed with slight pressure across the top of the forelimb to prevent vertical limb movements. Since the pig's forelimb and the force transducer were attached to the same baseboard, considerable movement of the board could occur without changing the response.

After the forelimb was fixed in the limb clamp, a hole 2 mm in diameter was drilled through the tip of the hoof of the third digit. A length of umbilical tape was threaded through the hole in the hoof and tied to the force transducer. A resting tension of 100 g, which produced maximum twitch tension, was placed on the toe by horizontal adjustment of the force transducer.

After attachment of the toe to the force transducer, the median nerve was located using a reference electrode consisting of a 25-gauge hypodermic needle inserted subcutaneously high in the axilla and a primary stimulating electrode consisting of a 17-gauge needle inserted between the epicondyles of the humerus

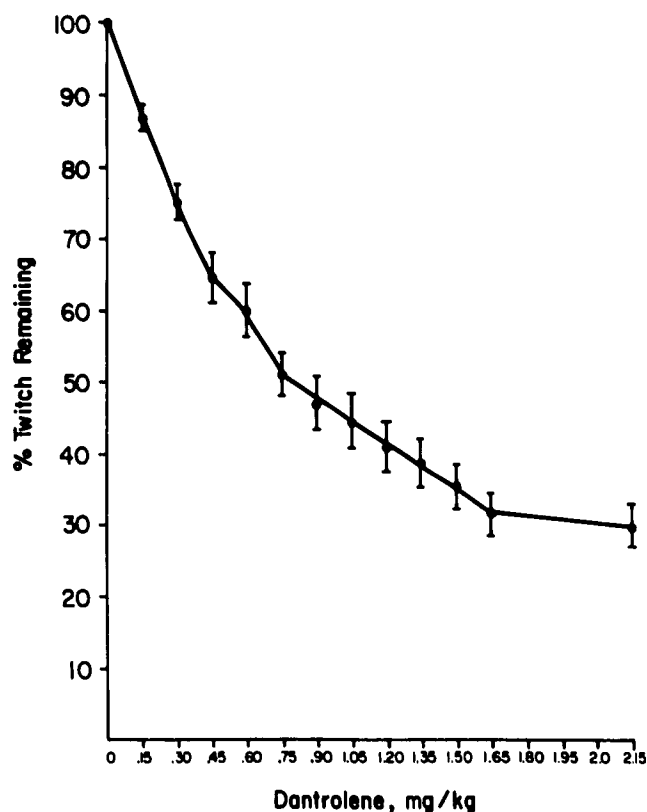


FIG. 2. Effects of dantrolene on indirectly stimulated toe twitch in MHS pigs. Dantrolene was administered intravenously at the rate of 0.15 mg/kg 2 min⁻¹. Values are means for six MHS pigs, and vertical bars are standard errors.

where an arterial pulse was palpable. The stimulating needle was inserted at this point with 20 volts applied for a duration of 0.02 msec. Median-nerve stimulation was evident as a distinct flexion of the toe without evidence of direct muscle stimulation. After location of the median nerve, the 17-gauge needle was held in place while a strand of 00 surgical steel wire was threaded through the needle. Stimulating voltage was then applied to the surgical wire to assess contact with the nerve, while the 17-gauge needle was removed from the field. After optimal position of the stimulating wire electrode had been obtained, as evidenced by maximal twitch response, the surgical wire was carefully bent at a right angle adjacent to the skin and sutured in place at this point. The signal from the force transducer was amplified and recorded by conventional techniques.

The first experimental series involved a dose-response effect of dantrolene on twitch tension. Dantrolene for intravenous administration was prepared fresh daily from powdered dantrolene supplied by Norwich Pharmacal Company as follows. One gram of dantrolene was dissolved in 1 l of water containing

0.113 g NaOH and 43.4 g mannitol. Dantrolene was administered via an ear vein as a 0.15-mg/kg bolus at 2-min intervals, a period during which the dantrolene effect on twitch reached steady state.

Three weeks after the dantrolene series, the effect of procainamide on skeletal muscle twitch was investigated in four of the six MHS pigs used for the dantrolene study. Procainamide was administered in a dosage similar to that used by Gronert *et al.*¹⁰ An initial dose of 4 mg/kg/two min was followed by ten doses of 1 mg/kg/min each.

Biopsy specimens of vastus lateralis muscle were obtained from two members of a family susceptible to malignant hyperthermia during anesthesia with nitrous oxide-narcotic. Muscle strips were prepared and tested as previously described.¹⁸ The effects of procainamide and dantrolene on the abnormal contracture response of MHS muscle were tested by adding these drugs to the muscle buffer before or after addition of halothane.

Results

Dantrolene was effective in blocking indirect toe twitch in MHS pigs (fig 2). The ED₅₀ for dantrolene was 0.85 mg/kg in MHS pigs. The final cumulative dose of 2 mg/kg resulted in 68 per cent block of the twitch response.

Procainamide to and including a final cumulative dose of 14 mg/kg had no effect on indirect toe twitch. The average twitch tension before addition of procainamide was 23.9 g ± SD = 5.9; after procainamide, 14 mg/kg, twitch was 23.6 g ± SD = 5.2. No evidence of hypotension or myocardial toxicity was observed in the MHS pigs during or after procainamide administration by this method.

The two patients from an MHS family were diagnosed as MHS-positive based on an abnormal caffeine-contraction dose response and the occurrence of halothane-induced contractures in isolated muscle strips. For comparative purposes, the caffeine-contraction dose response of normal vastus lateralis human muscle is presented (fig. 3, panel A). Normal human muscle responds to 1 mM caffeine with twitch potentiation, and a contracture response exceeding 1 g occurs only after 8 mM caffeine. In contrast to normal muscle, the MHS muscle had contracture initiated by 0.5 mM caffeine, and a contracture exceeding 1 g was evident after only 1 mM caffeine treatment (fig. 3, panel B). The main effect of halothane on normal muscle *in vitro* is twitch potentiation, with only minute contracture response (fig. 3, panel C). Muscle from the MHS patient responded to halothane with a marked contracture response, but without twitch potentiation (fig. 4, panel A). When this halo-

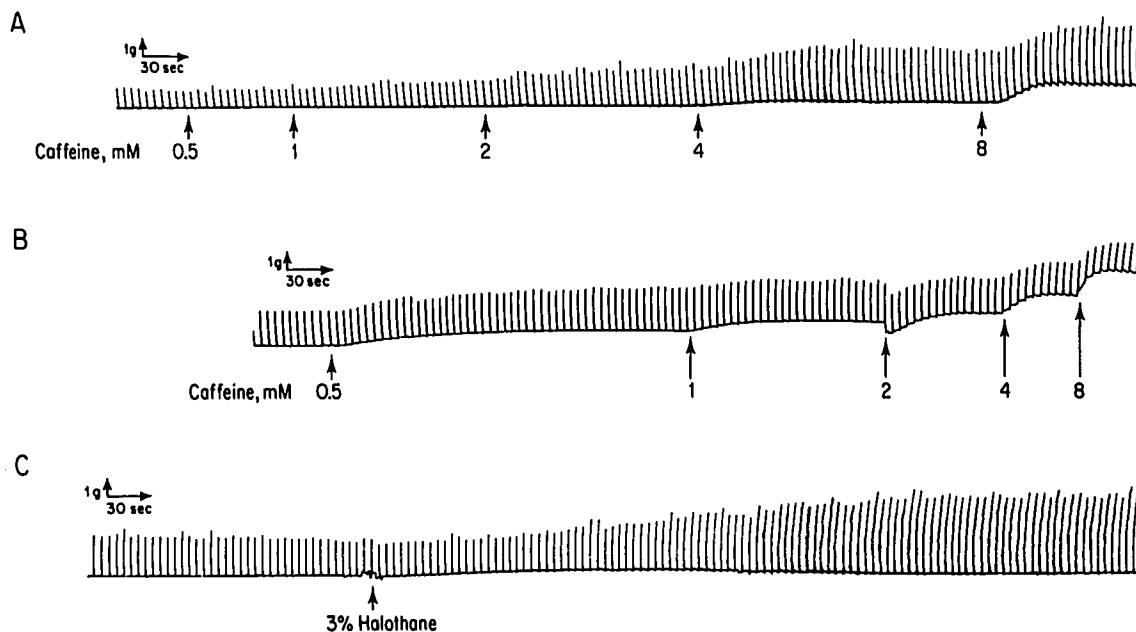


FIG. 3. The responses of normal and MHS human skeletal muscle to caffeine and halothane *in vitro*. *Panel A* shows a typical caffeine dose response for normal human muscle. In *panel B* the abnormal response of MHS human muscle to caffeine is demonstrated by contracture at the lower (0.5–2 mM) caffeine concentrations. The effect of halothane on normal muscle is demonstrated in *panel C*, where the response is twitch potentiation and minute contracture.

thane-induced contracture reached a peak, addition of dantrolene, 3 μ M, resulted in a reversal of the halothane-induced contracture and a slight potentiation of the twitch. A separate MHS muscle strip was treated

with dantrolene, 3 μ M, which resulted in a 73 per cent decrease of twitch tension (fig. 4, *panel B*). When this muscle strip was exposed to halothane, 3 per cent, it responded more like normal muscle, *viz.*, a minute

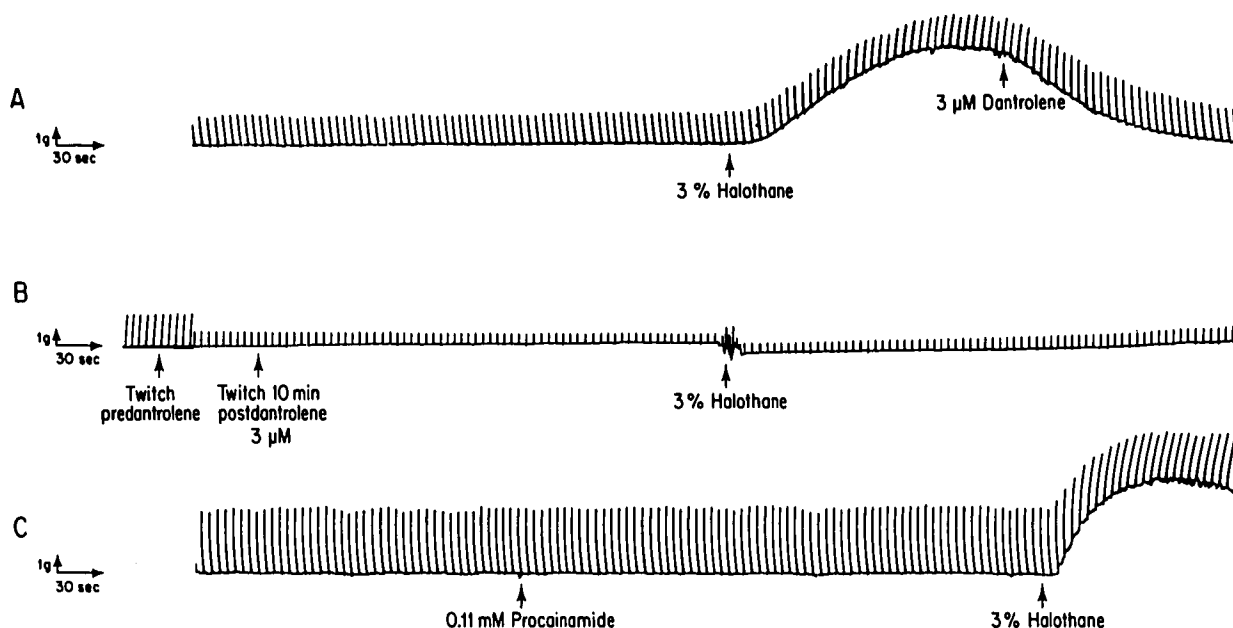


FIG. 4. The effects of dantrolene and procainamide on halothane-induced contracture of MHS human skeletal muscle. *Panel A* shows the abnormal halothane-induced contracture of MHS muscle. Addition of dantrolene at the contracture peak reversed the contracture response. *Panel B:* A MHS muscle was treated with dantrolene, which decreased the twitch response. Addition of halothane to the dantrolene-depressed muscle does not produce contracture. *Panel C:* Pretreatment of MHS muscle with procainamide had no effect on twitch response and did not block the contracture response to halothane.

contracture and twitch potentiation (fig. 4, *panel B*). Another individual muscle strip was treated with procainamide, 0.11 mM, which had no effect on basal twitch or on the contracture response to 3 per cent halothane (fig. 4, *panel C*).

Discussion

Results of these experiments support previous indications^{11,12} that procainamide is therapeutically and prophylactically ineffective for malignant hyperthermia. In other studies we have demonstrated that twitch potentiation followed by contracture precedes increases in rectal temperature and end-tidal carbon dioxide tension during halothane-induced malignant hyperthermia in the pig (unpublished results). These observations support the thesis that an abnormal increase in myoplasmic calcium is a primary etiologic event for malignant hyperthermia.¹³ The early response of twitch potentiation during malignant hyperthermia may relate to perturbations of the excitation-contraction coupling system causing increased calcium release with each action potential. The proposed site of action of dantrolene is on the excitation-contraction coupling system.¹⁷ The prophylactic effectiveness of dantrolene *in vivo* and *in vitro* for malignant hyperthermia responses suggests a lesion of excitation-contraction coupling for MHS muscle.

Procainamide in clinical doses had no effect *in vivo* or *in vitro* on normal twitch response or on the abnormal response to halothane. These results do not support a prophylactic or therapeutic role for procainamide in malignant hyperthermia as regards the abnormal skeletal muscle responses. The usefulness of procaine or procainamide for treatment of cardiac abnormalities with malignant hyperthermia is not precluded by these results.

The effects of dantrolene and procainamide on MHS human muscle *in vitro* coincide with effects observed *in vivo* in MHS pigs. It is concluded, therefore, that dantrolene should be effective in preventing or treating malignant hyperthermia during general anesthesia. These conclusions should not be construed to suggest that MHS patients pretreated with dantrolene can be given any anesthetic without risk.

Under any circumstances, only those anesthetic agents proven safe for MHS patients should be administered.

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